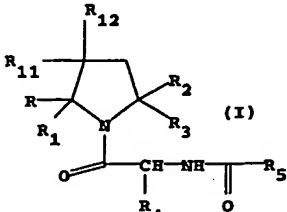
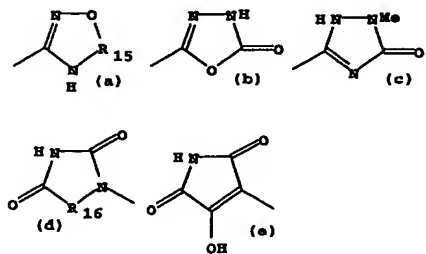


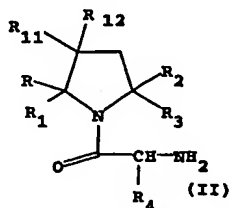
<p>94-242600/30 B03 RHONE POULENC RORER SA 93.01.07 93FR-000078 (94.07.08) C07D 207/08, A61K 31/40 New pyrrolidine derivs. with affinity for cholecystokinin and gastrin receptors - are used to treat e.g. psychosis, anxiety, irritable colon syndrome, tumours and pancreatitis. C94-110768 Addnl. Data: CAPET M, DUBROEUQ M</p>	<p>RHON 93.01.07 FR 2700166-A1 B(5-B1A, 6-D1, 6-D2, 7-D3, 14-C1, 14-D2B, 14-E8, 14-E10C, 14-E11, 14-E12, 14-H1B, 14-J1A1, 14-J1A3, 14-J1A4, 14-J1B3, 14-J1B4, 14-M1A, 14-M1C) .10</p>
<p>Pyrrolidine derivs. of formula (I) and their salts and isomers are new:</p>  <p>(I)</p>	<p>R = 1-12C alkyl, 3-12C cycloalkyl or 6-12C polycycloalkyl (all opt. mono or polyunsatd); phenylalkyl (opt. ring-substd. by alkyl, alkoxy and/or halo); diphenylalkyl; cinnamyl; pyridyl, furyl, thienyl, quinolyl, naphthyl or indolyl (all opt. substd. by one or more alkyl); or phenyl (opt. substd. by halo, alkyl, alkoxy, OH, NO₂, amino, mono- or di alkylamino, alkoxy carbonyl, CONR₇R₈, NHCOMe, CF₃, Ph and/or OCF₃); R₁, R₃, R₄ = H or alkyl; R₂ = (CH₂)_n-COR₆, (CH₂)_mOCOR₆, -(CH₂)_mNR₉R₁₀ or oxazoliny (opt. substd. by alkyl, and/or alkyl-3-oxadiazolyl); R₅ = phenyl (opt. substd. by halo, alkyl, alkoxy, and/or alkylthio), or naphthyl, indolyl, quinolyl, or phenylamino (all opt. phenyl-substd. by halo, alkyl, alkoxy, alkylthio, CF₃, COOH, alkoxy carbonyl, OH, NO₂, amino, acyl, CN, sulphamoyl, carbamoyl, hydroxyimino alkyl, alkoxyiminoalkyl, hydroxyamino carbonyl, alkoxyaminocarbonyl, tetrazol-5-yl, tetrazol-5-ylalkyl, trifluoromethylsulphonamido, alkylsulphiny, mono- or polyhydroxyalkyl, sulpho, alk-O-CO-alk, alk-COOX,</p> <p style="text-align: right;">FR 2700166-A+</p>

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<p>alk-O-alk, alk¹-COOX, O-alk-COOX, CH=CHCOOX, COCO₂X, alkSO₃H (or its salt), CH=CH-alk¹, C(=NOH)CO₂X, S-alk-CO₂X, SO-alk-CO₂X, SO₂-alk-CO₂X, OCH₂alk¹-COOX, CX=NO-alk-CO₂X, alk-N(OH)-CO-alk, alkSO₂H, SO₂NHCO₂R₁₃, SO₂NHSO₂R₁₃, CONHCO₂R₁₃, CONHSO₂R₁₃, B(OH)₂, C(NH₂)=NOH, SO₂NHR₁₄, CONHR₁₄, 2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl or a gp. of formula (a)-(e):</p>  <p>R₆ = OH, alkoxy, cycloalkoxy, cycloalkyl-alkoxy, phenyl or NR₉R₁₀;</p>	<p>R₆ = alkoxy, cycloalkoxy, cycloalkylalkoxy, phenyl or NR₉R₁₀; R₇ = H, alkyl, phenylalkyl or phenyl (opt. substd. by halo, alkyl, alkoxy and/or alkylthio); R₈ = alkyl, phenylalkyl or phenyl (opt. substd. by halo, alkyl, alkoxy and/or alkylthio); or NR₇R₈ = mono- or polycyclic opt. unsatd. heterocyclyl contg. 4-9C atoms and one or more O or N atoms and opt substd. by one or more alkyl; R₉ = H, alkyl, cycloalkylalkyl, cycloalkyl, phenylalkyl or phenyl (opt. substd. by halo, alkyl, alkoxy, and/or alkylthio); R₁₀ = alkyl, cycloalkyl, cycloalkylalkyl; phenylalkyl, or phenyl (opt. substd. by halo, alkyl, alkoxy and/or alkylthio); or NR₉R₁₀ = mono- or polycyclic opt. unsatd. heterocyclyl contg. 4-9C and one or more O, N and S, and opt. substd. by one or more alkyl; R₁₁ = H, alkyl or phenylalkyl; R₁₂ = alkyl, phenylalkyl, phenylsulphonyl, (CH₂)_pCOR₁₇, CN, CXO, CX=NOH, CX=NOalkCOOX, CHXOH, CHXOCOalk, NH₂ or NHCOalk; R₁₃ = alkyl, cycloalkyl, CF₃, or phenyl (opt. substd. by CN, NO₂, amino, halo and/or alkoxy); R₁₄ = tetrazol-5-yl;</p> <p style="text-align: right;">FR 2700166-A+/1</p>
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<p>94-242600/30</p> <p>R₁₅ = CO or SO; R₁₆ = O or CO; R₁₇ = OH, alkoxy, cycloalkoxy, cycloalkylalkoxy, phenyl, phenylalkoxy, alkyl or NR₉R₁₀; n = 0-2; m = 1 or 2; p = 0 or 1; X = H, alkyl, or phenyl alkyl; alk = alkyl or alkylene; and alk¹ = hydroxyalkyl, hydroxyalkylene, alkoxyalkyl or alkoxyalkylene; unless otherwise stated all alkyl moieties contain 1-4C; acyl contain 2-4C; and cycloalkyl contains 3-6C.</p> <p>USE</p> <p>(I) have strong affinity for cholecystokinin (CCK) and gastrin receptors. They are particularly useful in the treatment and prevention of disorders due to CCK and gastrin in the nervous system and GI tract. They are used to treat and prevent psychoses, anxiety, depression, neurodegeneration, panic attacks, Parkinson's disease, tardive dyskinesia, irritable bowel syndrome, pancreatitis, ulcers, intestinal motility disorders, certain tumours sensitive to CCK,</p>	<p>memory dysfunction, chronic withdrawal and abuse of alcohol or drugs, as pupil constrictors, analgesics or as potentiators for analgesics (both narcotic and non narcotic), and as appetite regulators.</p> <p>DOSAGE</p> <p>Dose is pref. oral at 0.05-1g/day in unit doses of 10-500 mg.</p> <p>ADVANTAGE</p> <p>(I) have low toxicity e.g. LD₅₀ of more than 40 mg/kg in mice.</p> <p>PREPARATION</p> <p>4 methods are claimed e.g. as follows: (a) (I; R₃=R₃¹) is prepd. by reacting a carbamic acid deriv. obtd. opt. in situ by reaction of a carbonic acid deriv. chosen from N,N'-diimidazolecarbonyl, phosgene, triphosgene and p nitrophenylchloroformate with a pyrrolidine cpd. of formula (II), with an aniline deriv. where the phenyl ring is opt. substd. by Q, and opt. salifying.</p> <p style="text-align: right;">FR 2700166-A+/2</p>
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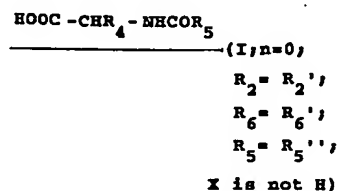
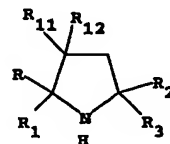


R_3^1 = phenylamino (opt. ring substd.)

Q = halo, alkyl, alkoxy, alkylthio, CF_3 , $COOH$, alkoxycarbonyl, OH, NO_2 , amino, acyl, CN, sulphonamoyl, carbamoyl, hydroxyiminoalkyl, alkoxyiminoalkyl, hydroxyaminocarbonyl, alkoxyaminocarbonyl, tetrazol-5-yl, tetrazol-5-ylalkyl, trifluoromethylsulphonamido, alkylsulphonyl, mono- or polyhydroxyalkyl, S, alk OCOalk, alkCOOX, alk-O-alk, alk¹-COOX, O-alkCOOX, CH=CHCOOX, COCO₂X, alkSO₃H (as its salt), CH=CH-alk¹, C(=NOH)-COOX, S-alkCO₂X, SO-alk-COOX, SO₂-alk-COOX, OCH₂-alk¹-COOX,

CX=NO-alk-CO₂X, alk-N(OH)-CO-alk, 2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl, alkSO₂H, SO₂NHCOR₁₃, SO₂NHSO₂R₁₃, CONHCOR₁₃, CONHSO₂R₁₃, B(OH)₂, C(NH₂)=NOH, SO₂NHR₁₄, CONHR₁₄ or a gp. (a)-(e).

(b)



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$R_2^1 = (CH_2)_nCOR_6$;

R_6^1 = alkoxy, cycloalkoxy or cycloalkylalkoxy;

R_3^{11} = phenyl (opt. substd.) naphthyl, indolyl, quinolyl or phenylamino (opt. ring substd. by halo, alkyl, alkoxy, alkylthio, CF_3 , NO_2 , acyl, CN, sulphonamoyl, alkoxycarbonyl, carbamoyl, alkoxyiminoalkyl, alkoxyaminocarbonyl, alk-O-CO-alk, CH=CH-alk¹, alk-O-alk, trifluoromethylsulphonamido, alkSO₃H (or its salt), O-alkCOOX, CH=CHCO₂X, COCO₂X, S-alkCO₂X, SO-alk CO₂X, SO₂alkCO₂X, OCH₂-alk¹-CO₂X, CX=NOalk-CO₂X, alkCO₂X or alk¹CO₂X); and

cpds. (I) may be interconverted.

EXAMPLE

A soln. of 0.32g tertbutyl 4-benzyl 5-phenyl 2-pyrrolidine carboxylate and 0.31g 2-(3-(3-benzoyloxycarbonyl-phenyl)ureido) acetic acid in 25ml acetonitrile was treated with 0.2g N,N'-dicyclohexylcarbodiimide at 20 ° C. The mixt. was stirred for 72 hrs. at 20 ° C. and worked up to give 0.54g (2S,4S,5R)tert-butyl-1-(2-(3-(3-benzoyloxycarbonylphenyl)ureido) acetyl)-4-benzyl-5-phenyl pyrrolidinecarboxylate.

A soln. of 0.54g. of this prod. in 25ml EtOAc was treated

with 0.1g 10% Pd/C. The suspension was stirred for 18 hrs. at 20 ° C. under H₂ (130KPa). The catalyst was filtered off and the mixt. was worked up and chromatographed to give 0.36g free acid.

In tests (I) have IC₅₀ value of < 1000nM for inhibition of binding to CCK receptors. (48pp1858DwgNo.0/0)

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